(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00585 A1

(51) International Patent Classification[7]: C07D 231/32, 231/30, A61K 31/4152, A61P 31/08, 37/06

(21) International Application Number: PCT/GB00/02513

(22) International Filing Date: 29 June 2000 (29.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9915184.7 29 June 1999 (29.06.1999) GB

(71) Applicant *(for all designated States except US)*: **A-VIRAL AS** [NO/NO]; Karihaugveien 102, N-1006 Oslo (NO).

(71) Applicant *(for GB only)*: **COCKBAIN, Julian** [GB/GB]; Flat 4, 83 Linden Gardens, London W2 4EU (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TJØTTA, Enok** [NO/NO]; A-Viral AS, Karihaugveien 102, N-1006 Oslo (NO). **KLAVENESS, Jo** [NO/NO]; A-Viral AS, Karihaugveien 102, N-1006 Oslo (NO).

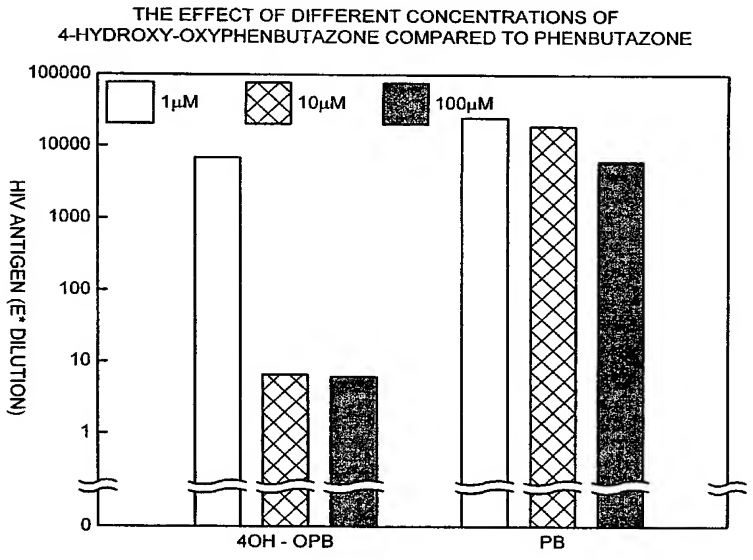
(74) Agents: **COCKBAIN, Julian** et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: PYRAZOLIDINOL COMPOUNDS



(57) Abstract: The invention provides the use of an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxopyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in therapy or prophylaxis. Additionally, the invention provides a method of combatting HIV infection which comprises administering to an HIV-infected patient a T-lymphocyte growth suppressing agent, preferably a pyrazolidinol, in an amount sufficient to suppress T-lymphocyte growth in said patient for a period sufficient to reduce the T-lymphocyte concentration in lymph nodes in said patient by at least 25 % said administration being repeated at intervals of at least 3 months.

WO 01/00585 A1

Published:

— *With international search report.*

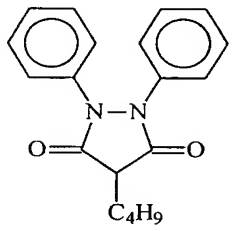
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

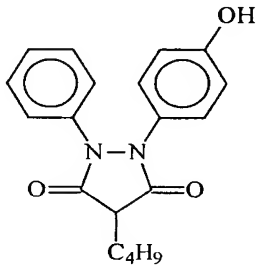
Pyrazolidinol Compounds

The present invention relates to certain pyrazolidinols and their sulphur (i.e. thio/thiol) analogs and pharmaceutical compositions thereof for use in antiviral, e.g. anti-HIV therapy and as anti-inflammatories and immunomodulators.

Phenbutazone and oxyphenbutazone are 1,2-bis aromatic-3,5-pyrazolidinediones which have been used as non-steroidal anti-inflammatory drugs (NSAIDs)



Phenbutazone (PB)



Oxyphenbutazone (OPB)

Other 3,5-pyrazolidinediones have likewise been proposed for use as NSAIDs (see for example US-A-3968219 (Rahtz)) and the hydroxy-protected enol forms have been proposed as pro-drug forms of phenbutazone and oxyphenbutazone (see US-A-4117232 (Bodor), US-A-3957803 (Bodor), US-A-4169147 (Bodor), US-A-4036845 (Bodor) and US-A-4139709 (Bodor)).

In US-A-4956377 (Miesch) it was proposed that this class of NSAIDs had utility as an antiviral agent, in particular for the treatment of HIV.

We have now surprisingly found that where the 4-carbon of the N_2C_3 ring carries an optionally protected

hydroxy or thiol group, the compounds have very significantly enhanced antiviral, in particular anti-HIV, efficacy.

Thus viewed from one aspect the invention provides the use of an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in therapy or prophylaxis.

Where a particular 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine may exist in more than one stereoisomeric form, it may be used in single isomer form or as an isomer mixture, e.g. a racemic mixture.

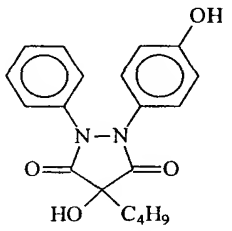
Viewed from a further aspect, the invention provides an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

Viewed from a still further aspect the invention provides a method of treatment of the human or non-human (e.g. mammalian, reptilian or avian) body to combat an inflammatory or viral disease, preferably an immuno-deficiency viral disease, in particular HIV, which method comprises administering to said body an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

Viewed from a still further aspect, the invention provides a pharmaceutical composition comprising an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, together with at least one pharmaceutically acceptable

carrier or excipient.

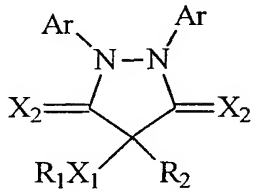
The applicants have found that oxyphenbutazone, as commercially available, contains minute quantities of certain impurities, presumably as a result of undesired oxidative breakdown. One of these, present at about 0.4% wt, is 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (hereinafter "4-OH-OPB"), i.e.



4 OH-OPB

4-OH-OPB is of course a compound according to the invention and thus it should be understood that references to the 4-hydroxy compounds of the invention, their use and compositions thereof should not be taken to include references to such compounds when in intimate admixture with overwhelmingly larger quantities of a 3,5-pyrazolidinedione which carries no optionally protected 4-hydroxy or 4-thiol group. By overwhelmingly larger is meant a relative weight ratio of at least 98:2. In general, the compounds of the invention should not desirably be used in intimate admixture with larger quantities (i.e. a relative weight ratio of more than 50:50) of such compounds carrying no O or S attached group at the 4-position, and more desirably they should not be used with such compounds present in greater than 10:90 weight ratio.

The compounds of the invention, hereinafter referred to as pyrazolidinols for convenience, will preferably be of formula I



(I)

(where each X_2, which may be the same or different is O or S, preferably O;
X_1 is O, OO or S, preferably O or S, most preferably O;
R_1 is hydrogen or a hydroxyl or thiol protecting group (e.g. an acyl group, preferably containing up to 6 carbons, e.g. an acyl group such as an alkylcarbonyl group, for example acetyl), preferably hydrogen;
R_2 is hydrogen or more preferably a carbon attached organic group containing up to 10 carbons, e.g. an alkyl, alkenyl, alkynyl, alkaryl, aralkyl or aralkenyl group, optionally substituted, e.g. by a sulphonyl group; and
each Ar, which may be the same or different, is a homo or heterocyclic aromatic group, optionally substituted, e.g. by C_{1-6} alkyl or alkoxy groups) or a salt thereof.

In the compounds of the invention 0, 1 or 2 of the X_1 and X_2 groups may be S. It is thought that it is especially preferred that one thio X_2 group be present.

In the compounds of the invention, the R_2 group is preferably other than hydrogen and may for example be straight chain, branched, cyclic or cyclic-attached-to-straight chain. Preferably it is an alkyl or alkenyl group, especially a C_{1-6} alkyl or alkenyl group, e.g. n-propyl, n-butyl, n-pentyl or 1-methyl-but-2-en-4-yl or an aralkyl (e.g. benzyl) or alkaryl (e.g. methylphenyl) or arylsulphonylalkyl (eg phenylsulphonylethyl) group.

Where R_1 in the compounds of the invention is other than hydrogen it is preferably a metabolically labile hydroxy- or thiol-protecting group which yields a physiologically tolerable R_1OH metabolite. Acyl groups are preferred in this regard.

In the compounds of formula I, where each X_2 is oxygen and one Ar is phenyl, the other Ar is preferably other than phenyl e.g. parahydroxyphenyl.

A wide range of hydroxy- and thiol-protecting groups however is known from the literature (see McOmie, "Protective groups in organic chemistry", Plenum, 1973

and Greene, "Protective groups in organic synthesis", Wiley Interscience, NY, 1981) and many compounds of formula I in which R_1 is a protecting group may be useful as intermediates in the production of compounds of formula I in which R_1 is hydrogen.

The Ar groups in the compounds of formula I are preferably 5 to 7 membered aromatic rings, optionally carrying a fused aromatic ring and optionally substituted on ring atoms, for example by C_{1-6} alkyl groups but especially by electron withdrawing substituents, e.g. hydroxy, thiol, phenyl, C_{1-6} alkoxy, cyano, halo (e.g. Cl, F, Br or I), protected hydroxy, or protected thiol. Ring heteroatoms will generally be selected from O, N and S, preferably with a single ring heteroatom in any aromatic Ar heterocycle. Ar is preferably phenyl optionally substituted, especially in the para-position by $-X_1-R_1$ or Cl (where $-X_1-R_1$ is as defined above). Especially preferably one Ar is phenyl and the other is p-hydroxy-phenyl.

Where the substitution of the pyrazolidinols of the invention is such that they may form addition salts with acids or bases, the addition salts which have physiologically tolerable counterions are of course preferred, e.g. sodium, organic amine, halides, phosphates, hydrogen carbonates, etc.

The pyrazolidinols of the invention may particularly advantageously be used in combination therapy with other antiviral, especially anti-HIV, agents, in particular reverse transcriptase inhibitors and/or protease inhibitors, e.g. zidovudine, didanovine, zalcitabine, stavudine, lamivudine, nevirapine, delavirdine, indinavir, ritonavir, nelfinavir, hydroxyurea kolchicine, AZT and 2',3'-dideoxyinosine (ddI). Such combination therapy forms a further aspect of the present invention.

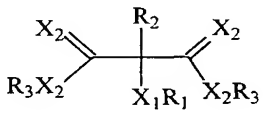
A drawback of traditional combination therapy, has often been that even under intensive antiviral treatment with a combination of drugs, a little HIV production

continues and is unaffected by treatment. The compounds of the invention may prove to have an effect in reducing this residual HIV production when given in combination with other antiviral agents. This may be due to the increasing antiviral effect which has been seen in long term cell culture experiments and which may counteract any development of resistance to the compounds.

The pyrazolidinols of the invention may be prepared by oxidation of a corresponding compound where R_1X_1 is replaced by hydrogen; by reaction of a corresponding compound where R_1X_1 is HX_1 with a hydroxy or thiol protecting agent to introduce a non-hydrogen R_1 group; or by condensation of a hydrazine derivative with an optionally protected 2-hydroxy-propane dioic acid ester (or a sulphur analog), e.g. by condensation of a compound of formula II

Ar - HN - NH - Ar (II)

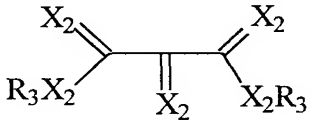
with a compound of formula III



(III)

where R_1, R_2, X_1, X_2 and Ar are as hereinbefore defined and X_2R_3 is a leaving group, for example where R_3 is an alkyl group, e.g. a C_{1-6} alkyl group.

Alternatively, a compound of formula II may be condensed with a compound of formula IV



(IV)

(where X_2 and R_3 are as defined above) and then reacted with an alkylating agent, e.g. $(R_2)_2Zn$ to produce a compound of formula I in which X_1R_1 is OH or SH.

For administration, the pyrazolidinols of the invention may be formulated in any convenient form, e.g. tablets, coated tablets (e.g. delayed release tablets), capsules, solutions, suspensions, dispersions, syrups, powders, sprays, suppositories, transdermal patches, gels, emulsions and creams. Administration may be via any convenient route, e.g. oral, rectal, transdermal, nasal, subcutaneous, intravenous, intramuscular, etc. Oral administration, e.g. of tablets or capsules is preferred. The pyrazolidinols may be formulated together with conventional pharmaceutical carriers, diluents or excipients, e.g. aqueous carriers (for example water for injections), binders, fillers, stabilizers, osmolality adjusting agents, effervescing agents, pH modifiers, viscosity modifiers, sweeteners, lubricants, emulsifiers, flavours, coating agents (e.g. gastric juice resistant coatings), etc. Where any formulation results in a loss of compound, this loss should be calculated and the dosage increased proportionally to obtain the desired active concentration.

The dosage of the pyrazolidinols given according to the invention will depend on the size and species of the subject being treated but will generally be in the range of 0.05 to 2000 mg/day, more particularly 0.5 to 1000 mg/day, especially 1 to 100 mg/day, preferably with administration being effected once, twice, three times or four times daily. For mice, doses of up to 2000 mg/kg (corresponding to 20 mM maximal concentration in extracellular fluid) could be given before lethal dosage was reached, ie effective treatment doses were up to 200000 times smaller than the lethal dose.

For regular, e.g. continuous daily treatment according to the invention, the daily dosage of the pyrazolidinol will preferably be in the range 5 nmol to 2 μmol/kg bodyweight, more preferably 100 nmol to 1.5 μmol/kg, especially 500 nmol to 1 μmol/kg.

Inhibition of virus production may be achieved by small intermittent doses of pyrazolidinol, and are expected to induce inhibition of the virus after a latency of about 11 weeks. Subsequently, inhibition may be expected to level out, should resistance to the compound develop. Such doses may be administered at a frequency of 1-14 days, preferably 7 days. The doses should be equivalent to a concentration in plasma/tissue fluid of from 100-1000 nM and may be obtained by ingestion or injection of from 0.7-7 mg in a 70 Kg human.

However, in a particularly preferred embodiment of the invention, a pyrazolidinol according to the invention is administered at a dose sufficient to suppress T-lymphocyte (CD4 and CD8 cell) growth (e.g. a daily dose of 0.1 to 10 μmol/kg) for a period of 1 to 14 days, preferably 2 to 7 days at intervals of at least 3 months, preferably at least 9 months, e.g. 10 to 18 months. In this way the patient's immune system may be "refreshed" by removal of the preponderance of T-lymphocytes directed to HIV antigens. Such a treatment indeed is novel and forms a further aspect of the invention. Viewed from this aspect the invention provides a method of combatting HIV infection which comprises administering to an HIV-infected patient a T-lymphocyte growth suppressing agent, e.g. a pyrazolidinol, in an amount sufficient to suppress T-lymphocyte growth in said patient for a period sufficient to reduce the T-lymphocyte concentration in the lymphatic system, e.g. the lymph nodes, in said patient by at least 25%, more preferably at least 50%, said administration being repeated at intervals of at least 3 months, preferably at least 9 months.

High tissue concentrations intended to give an immunomodulating effect should preferably be given for limited periods at doses of 1μM or above in plasma/tissue fluid. Such doses and lengths of

administration will vary according to the condition of each patient and may be decided with the guidance of tests such as the count of HIV memory subsets of T8 and T4. As stated above, the goal of treatment according to this aspect of the invention should be to reduce subsets which are found to be too prevalent without overly affecting naive T-cells.

In order to obtain the desired reduction of HIV specific lymphocytes (e.g. HIV memory CD8 and CD4 lymphocytes) without overly affecting naive T-lymphocytes or other essential blood cells, monoclonal antibodies against the unwanted subtypes may also be administered. Further, drugs such as kolchicine and/or hydroxy-urea may be included in the intermittent intensive treatment. Such additional drugs are anticipated to have a somewhat different immunomodulating effect to the compounds of the invention and so may be used advantageously in combination with pyrazolidinols for refreshing the immune system.

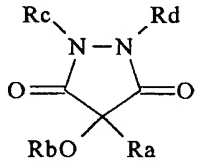
Besides HIV, the pyrazolidinols of the invention may be used to combat other viral infections, especially retroviral infections but also infections by togaviridea, reoviridea, picornaviridea, hantaviridea, orthomyxoviridea, paramyxoviridea, mononegaviralis, viral hepatitis, haemorrhagic fevers, flaviviridea, viral encephalitis, coronaviridea, calciviridea, adenoviridea, papovaviridea, arboviridea, pox virus, rhabdoviridea, herpes virus and arenaviridea. The pyrazolidinols of the invention may in particular be used to combat viral infections of CD4 cells, e.g. HIV-1, HIV-2, HTLV-I, HTLV-II and herpes viruses, for example to combat AIDS, T-cell tumours (e.g. Sezary Syndrome, mycosis fungoides and T-cell lymphoma, and particularly CD4 cell tumours), tropic spastic paraparesis, and Karposi's sarcoma. Moreover despite not being of the accepted formula for NSAIDs (which

would require an acid proton in place of R_1X_1 at the 4-position), they may be used as anti-inflammatory drugs. All these uses form aspects of the invention.

Due to the immunomodulating effect of the compounds of the invention, they are expected to have uses in control of other immune-system related diseases, such as auto immune diseases and as immunosuppressants. In particular, the compounds of the invention are expected to have a positive effect on the generation of autoimmune diseases, on developed autoimmune diseases and on diseases related to such diseases, such as Addison's disease, Behçet's syndrome, diabetes mellitus and other endocrine diseases, haemolytic anaemia, lupus erythematosus, multiple sclerosis, myasthenia gravis, pernicious anaemia, polyglandular deficiency, polymyositis, dermatomyositis, testicular failure, thrombocytopenic purpura, Crohns disease, ulcerative colitis, rheumatic disorders (e.g. rheumatoid arthritis) etc.

The effect of the compounds of the invention on the immune system may also be that of immunosuppression. Such an effect may be used, for example, to control rejection of a medical transplant or implant. In particular, the compounds may be used to reduce rejection following tissue or organ transplant.

Various 4-hydroxy-3,5-dioxo-pyrazolidines are known in the literature (although not for medical purposes such as HIV therapy). These are compounds of formula V



(V)

where R_a to R_d are as set out in Table 1 below:

Table 1

R_a	R_b	R_c	R_d
H	H	H	C_6H_5
H	H	C_6H_5	C_6H_5
CH_3	H	H	C_6H_5
CH_3	H	H	$-CH_2-C_6H_5$
CH_3	H	H	$p-CH_3O-C_6H_4$
CH_3	H	H	$p-Cl-C_6H_4$
C_2H_5	H	H	C_6H_5
C_2H_5	H	C_6H_5	C_6H_5
C_2H_5	H	H	N-methyl-piperidin-4-yl
iC_3H_7	H	H	C_6H_5
nC_3H_7	H	H	C_6H_5
nC_3H_7	H	C_6H_5	C_6H_5
nC_3H_7	H	H	5-phenyl-triazol-1-yl
C_4H_9	H	H	C_6H_5
C_4H_9	H	C_6H_5	C_6H_5
C_4H_9	H	C_6H_5	$p-OH-C_6H_4$
C_4H_9	OH	C_6H_5	C_6H_5
C_4H_9	OH	C_6H_5	$p-OH-C_6H_4$
C_4H_9	H	H	N-methyl-piperidin-4-yl
C_5H_{11}	H	H	C_6H_5
C_5H_{11}	H	C_6H_5	C_6H_5
C_5H_{11}	H	H	5-phenyl-triazol-1-yl
Cyclohexyl	H	H	C_6H_5
Phenyl	H	H	C_6H_5
Phenyl	H	C_6H_5	C_6H_5
Benzyl	H	H	C_6H_5
Benzyl	H	C_6H_5	C_6H_5
$CH_3CO(CH_2)_2$	H	C_6H_5	C_6H_5
$(CH_3)_2C=CH-$	H	C_6H_5	C_6H_5
$(CH_2)_2C=CHCH_2$	H	C_6H_5	C_6H_5
$C_6H_5SCH_2CH_2$	H	C_6H_5	C_6H_5
Pyrrolidin-1-yl	H	C_6H_5	C_6H_5
Piperidin-1-yl	H	C_6H_5	C_6H_5
Morpholin-4-yl	H	C_6H_5	C_6H_5

Such compounds are thus not claimed per se herein; however their use and pharmaceutical compositions containing them do form part of the scope of the invention.

The invention will now be illustrated further by the following non-limiting Examples and by reference to the Figures, in which:

Figure 1 shows the HIV antigen concentration in human CD4 cells infected with HIV and treated with 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (4OH-OPB) or phenbutazone (PB) at various concentrations;

Figure 2 shows the effect of 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (4OH-OPB) when used in combination with AZT;

Figure 3 shows the effect of 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (4OH-OPB) when used in combination with indinavir; and;

Figure 4 shows the effect of 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (4OH-OPB) when used in combination with nevirapine;

A similar effect to those shown in figures 2-4 is seen when OPB is used in combination with 2',3'-dideoxyinosine (daI).

EXAMPLE 1

Preparation of *4-Methoxyazobenzene*

A mixture of 4-phenylazophenol (9.9g; 50 mmol), iodomethane (7.1 g; 50 mmol), potassium carbonate (6.9 g; 50 mmol), and acetone (100 ml) was refluxed 48 h. After evaporating off the solvent, the residue was dissolved in water (25 ml), diethyl ether (50 ml) and THF (30 ml). The aqueous layer was extracted with ether (3 × 20 ml) and the combined organic solutions were washed with saturated NaCl solution (1 × 20 ml) and

dried ($MgSO_4$). After filtration and evaporation, the residue was recrystallized from 96% ethanol to give 8.7 g (82%).

EXAMPLE 2

Preparation of 1-(4-Methoxyphenyl)-2-phenylhydrazine

Zinc powder (10.0 g; 0.15 mol) was added to a stirred mixture of 4-methoxyazobenzene (4.24 g; 20.0 mmol) in 96% ethanol (75 ml) and saturated NH_4Cl solution (2.0 ml) at 0 °C (bath temperature). Two more portions of saturated NH_4Cl solution (2.0 ml) were added at 1.5 h intervals. The yellowish solution was poured into cold water (100 ml) and filtered. The residue was extracted with methylene chloride (5 × 50 ml). The combined aqueous phases were extracted with methylene chloride (3 × 25 ml). The combined organic solutions were dried (Na_2SO_4), filtered, and evaporated to give 4.3 g crude 1-(4-methoxyphenyl)-2-phenylhydrazine as a reddish oil.

EXAMPLE 3

Preparation of 4-(1-Butyl)-1-(4-methoxyphenyl)-2-phenyl-3,5-pyrazolidinedione

Diethyl butylmalonate (4.33 g; 20.0 mmol) was added to a stirred solution of sodium (0.46 g; 20.0 mmol) in absolute ethanol (20 ml), followed by crude 1-(4-methoxyphenyl)-2-phenylhydrazine (4.3 g; 20 mmol max.) in absolute ethanol (5 ml). About 2/3 of the ethanol was distilled off and xylene (20 ml) was added to the residue. The reaction mixture was heated to 140-145 °C (bath temperature) for 15 h to distill off the rest of the ethanol. The reaction mixture was cooled to 0 °C (bath temperature) and poured into ice water (ca. 100 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 15

ml); the extracts were discarded. The cold aqueous layer was acidified with 6 M HCl (5 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The combined extracts were washed with water (2 × 10 ml) and dried ($MgSO_4$). Filtration and evaporation gave 3.84 g amber oil. Purified by flash chromatography on a 130 × 65 mm silica gel 60 column eluted with ethyl acetate-heptane (1:3) to give 1.45 g (21%) colourless oil.

^{1}H NMR (200 MHz; $CDCl_3$): δ 0.90 (3H, t, *J* = 7.5 Hz), 1.25-1.6 (4H, m), 2.0-2.15 (2H, m), 3.37 (3H, t, *J* = 6.0 Hz), 3.69 (3H, s), 6.81 (2H, d, *J* = 8.4 Hz), 7.22 (2H, d, *J* = 8.6 Hz), 7.1-7.35 (5H, m).

^{13}C NMR (50 MHz; $CDCl_3$): δ 13.6, 22.2, 27.5, 27.6, 45.6, 54.7, 112.9, 121.6, 123.3, 125.4, 127.1, 127.4, 133.9, 156.5, 168.2, 168.7.

EXAMPLE 4

Preparation of 1,2-Diphenyl-4-(4-methylphenyl)-3,5-pyrazolidinedione

Prepared from 1,2-diphenylhydrazine (3.70 g; 20.0 mmol), diethyl 2-(*p*-tolyl)malonate (5.0 g; 20.0 mmol), and sodium (0.46 g; 20.0 mmol) using the procedure of Example 3. The crude product crystallized on standing and was recrystallized twice from absolute ethanol to give 1.22 g (18%), mp 184-185 °C.

^{1}H NMR (200 MHz; $CDCl_3$): δ 2.31 (3H, s), 4.51 (1H, s), 7.1-7.4 (14H, m).

^{13}C NMR (50 MHz; $CDCl_3$): δ 21.1, 51.9, 122.7, 126.9, 128.3, 129.0, 129.9, 135.8, 138.3, 168.6.

EXAMPLE 5

Preparation of 4-Benzyl-1,2-diphenyl-3,5-pyrazolidinedione

Prepared from 1,2-diphenylhydrazine (4.60 g; 25.0 mmol), diethyl benzylmalonate (5.0 g; 20 mmol), and sodium (0.46 g; 20.0 mmol) using the procedure of Example 3. The crude product was recrystallized from absolute ethanol to gave 3.51 g (50%), mp 136-137 °C [lit. 137-138 °C (Beil. III/IV, **24**, 1463)].

^{1}H NMR (200 MHz; $CDCl_3$): δ 3.41 (2H, d, *J* = 4.6 Hz), 3.63 (1H, t, *J* = 5.0 Hz), 6.85-7.3 (10H, m).

^{13}C NMR (50 MHz; $CDCl_3$): δ 33.9, 48.5, 123.2, 126.9, 127.3, 128.6, 128.7, 129.9, 135.2, 135.4, 169.3.

EXAMPLE 6

Preparation of 4-Allyl-1,2-diphenyl-3,5-pyrazolidinedione

Prepared from 1,2-diphenylhydrazine (5.2 g; 28.0 mmol), diethyl allylmalonate (5.0 g; 25.0 mmol), and sodium (0.58 g; 25.0 mmol) using the procedure of Example 3. The crude product was recrystallized from absolute ethanol to give 2.21 g (30%) tan crystals, mp 135-137 °C.

^{1}H NMR (200 MHz; $CDCl_3$): δ 2.82 (2H, t, *J* = 6.0 Hz), 3.46 (2H, t, *J* = 5.4 Hz), 5.1-5.3 (2H, dd), 5.7-5.95 (1H, m), 7.1-7.3 (10H, m).

^{13}C NMR (50 MHz; $CDCl_3$): δ 31.7, 46.4, 119.9, 122.7, 126.8, 128.9, 131.7, 135.6, 169.5.

EXAMPLE 7

Preparation of 4-(1-Butyl)-4-hydroxy-1-(4-hydroxyphenyl)-2-phenyl-3,5-pyrazolidinedione (4OH-OPB)

Method A

Oxyphenbutazone.H_2O (1 mmol), 30% H_2O_2 (0.7 mL), 1N NaOH (0.1 mL) and methanol (3.5 mL) are allowed to stand for 13 hours at ambient temperature. The mixture is then poured into 5% HCl (20 mL) and extracted with ethyl acetate (2 x 20 mL). The ethyl acetate phase is separated, dried over sodium carbonate and the solvent is removed under reduced pressure without heating. The residue is subjected to flash chromatography (silica/ ethyl acetate). The title product is recrystallized from ethyl acetate.

Method B

A solution of oxyphenbutazone hydrate (2.0 g; 5.8 mmol), 35% hydrogen peroxide solution (3.4 ml; 40 mmol), and 1 M sodium hydroxide solution (0.6 ml; 0.6 mmol) in methanol (20 ml) was allowed to stand for 24 h at ambient temperature. The mixture was acidified with 1 M HCl solution (50 ml) and extracted with ethyl acetate (4 × 15 ml). The combined extracts were washed with saturated NaCl solution (1 × 10 ml) and dried ($MgSO_4$). After filtration and evaporation, the residue was purified by flash chromatography on a 100 × 65 mm silica gel 60 column eluted with ethyl acetate-heptane (1:1), taking 50-ml fractions, giving 1.3 g (66%).

^{1}H NMR (200 MHz; $CDCl_3$): δ 0.88 (3H, t, J = 6.6 Hz), 1.25-1.5 (4H, m), 1.95-2.05 (2H, m), 6.49 (1H, br s), 6.75 (2H, d, J = 8.9 Hz), 7.12 (2H, d, J = 8.9 Hz), 7.1-7.35 (5H, m).

^{13}C NMR (50 MHz; $CDCl_3$): δ 13.6, 22.3, 24.3, 36.2, 72.8, 114.3, 121.9, 123.8, 125.3, 125.7, 127.2, 133.5, 154.6, 169.0, 169.5.

EXAMPLE 8

Preparation of 4-(1-Butyl)-4-hydroxy-1-(4-

methoxyphenyl)-2-phenyl-3,5-pyrazolidinedione

Prepared from 4-(1-butyl)-1-(4-methoxyphenyl)-2-phenyl-3,5-pyrazolidinedione (1.35 g; 3.8 mmol), 35% H_2O_2 (4.3 ml; 50 mmol), 2 M NaOH (0.35 ml; 0.7 mmol), and methanol (50 ml) using the procedure of Example 7. Purified by flash chromatography on a 110 × 65 mm silica gel 60 column eluted with ethyl acetate-heptane (1:1) to give 0.7 g (52%).

^{1}H NMR (200 MHz; $CDCl_3$): δ 0.85 (3H, t, *J* = 6.2 Hz), 1.2-1.5 (4H, m), 2.0-2.1 (2H, m), 3.69 (3H, s), 4.8 (1H, br s), 6.77 (2H, d, *J* = 9.0 Hz), 7.19 (2H, d, *J* = 9.0 Hz), 7.1-7.35 (5H, m).

^{13}C NMR (50 MHz; $CDCl_3$): δ 13.5, 22.3, 24.3, 36.7, 54.7, 73.3, 113.0, 122.1, 123.8, 125.8, 126.1, 127.5, 133.0, 156.7, 168.5, 169.0.

EXAMPLE 9

Preparation of 1,2-Diphenyl-4-hydroxy-4-[2-(phenylsulfonyl)ethyl]-3,5-pyrazolidinedione

Prepared from (±)-sulfinpyrazone (2.02 g; 5.0 mmol), 35% H_2O_2 (4.3 ml; 50 mmol), 2 M NaOH (0.35 ml; 0.7 mmol), and methanol (50 ml) using the procedure of Example 7. Purified by flash chromatography on a 130 × 65 mm silica gel 60 column eluted with ethyl acetate-acetic acid (20:1) to give 80 mg (4%).

^{1}H NMR (200 MHz; $CDCl_3$): δ 2.1-2.5 (2H, m), 3.0-3.7 (2H, m), 5.5 (1H, br s), 6.4-7.9 (15H, m).

^{13}C NMR (50 MHz; $CDCl_3$): δ 28.7, 47.5, 70.2, 121.5, 122.9, 125.8, 126.5, 127.4, 127.7, 127.9, 129.9, 133.3, 133.4, 136.9, 139.2, 167.5, 168.0.

EXAMPLE 10

1,2-Diphenyl-4-hydroxy-4-(4-methylphenyl)-3,5-

pyrazolidinedione

A mixture of 1,2-diphenyl-4-(4-methylphenyl)-3,5-pyrazolidinedione (1.10 g; 3.2 mmol), 35% H_2O_2 (0.47 ml; 5.5 mmol), and acetic acid (40 ml) was stirred 16 days at room temperature. Sodium metabisulfite (1.0 g) was added and excess acetic acid evaporated off. The residue was dissolved in hot ethyl acetate (25 ml) and benzene (25 ml) and filtered. After cooling to room temperature, the mixture was filtered and the residue recrystallized from 50% aqueous ethanol (20 ml) to give 0.58 g (53%).

^1H NMR (200 MHz; $CDCl_3$: δ 2.32 (3H, s), 7.0-7.45 (14H, m).

^{13}C NMR (50 MHz; $CDCl_3$): δ 21.1, 57.9, 123.9, 124.5, 127.0, 128.3, 128.4, 128.7, 130.4, 135.6, 139.0, 168.5.

EXAMPLE 11

Preparation of *4-Benzyl-1,2-diphenyl-4-hydroxy-3,5-pyrazolidinedione*

Prepared from 4-benzyl-1,2-diphenyl-3,5-pyrazolidinedione (3.3 g; 9.6 mmol), 35% H_2O_2 (1.4 ml; 16.3 mmol), and acetic acid (50 ml) using the procedure of Example 10 to give 1.0 g (30%).

^1H NMR (200 MHz; $CDCl_3$): δ 3.30 (2H, s), 6.75-7.3 (15H, m).

^{13}C NMR (50 MHz; $CDCl_3$): δ 43.1, 75.4, 123.0, 126.7, 127.5, 128.4,, 130.2, 132.1, 134.7, 170.1.

EXAMPLE 12

Antiviral activity of 4OH-OPB (Example 7)

4OH-OPB was added to cultures of growing MT4 cells (a

human CD4 cell line). HIV-1, stored in the culture medium at -75°C was thawed and added in an amount which infected about 1 in 7 cells in each culture. The virus was absorbed to the cells for 2.3 hours at ambient temperature whereafter the cultures were centrifuged at 1200 rpm, the medium was removed, the cells were suspended in fresh growth medium and 4OH-OPB was added to concentrations of 1, 10 and 100 μM (diluted in medium from a stock solution of 20 mM in DMSO). After 72 hours the HIV antigen concentration was determined using Abbott's test. By way of comparison phenbutazone (PB) was tested analogously. The results are shown in Figure 1 and demonstrate inhibition of virus production by 4OH-OPB at concentrations above the lowest tested.

EXAMPLE 13

Combination Antiviral effect with 4OH-OPB

Cell culture experiments were carried out as in Example 12, but in place of 4OH-OPB (0-100 μM) was added:

i) 4OH-OPB (0-10 μM) with AZT (0-1 μM)
ii) 4OH-OPB (0-100 μM) with Indinavir (0-100 μM)
iii) 4OH-OPB (0-100 μM) with Nevirapin (0-10 μM)
iv) 4OH-OPB (0-10 μM) with ddI (0-100 μM)

The results are shown in Figures 2-5 respectively and demonstrate the enhanced anti-HIV effect of 4OH-OPB in combination with other anti-viral agents.

EXAMPLE 14

Preparation of capsules for oral use

4-OH OPB (Example 7)	50 mg
Amylum maydis	q.s.

The powder is mixed and filled into hard gelatin capsules (Capsugel size 00).

EXAMPLE 15

Preparation of tablets

	Gram
4-OH OPB (Example 7)	200
Lactose	85
Polyvinylpyrrolidone	5
Starch	42
Talcum powder	15
Magnesium stearate	3

4-OH OPB and lactose are screened through a 0.15 mm sieve and mixed together with an aqueous solution of polyvinyl-pyrrolidone. The mass is granulated, and the dried (40°C) granulate is mixed with starch, talcum powder and magnesium stearate. The granulate is compressed into tablets. The tablet diameter is 11 mm, the tablet weight is 350 mg and each tablet contains 200 mg 4-OH OPB.

EXAMPLE 16

Preparation of a suspension for rectal administration

Methyl p-hydroxybeznzoate (70 mg) and propyl-p-hydroxybenzoate (15 mg) are dissolved in water (100 ml) at 90°C. After cooling to 30°C, methyl cellulose (2g) is added and the mixture is agitated for 3 hours. 1 gram 4-OH OPB (Example 7) is screened through a 0.15 mm sieve, and dispersed in the solution under vigorous stirring. The suspension is filled in a 100 ml tube. The suspension contains 10 mg 4-OH OPB/ml.

EXAMPLE 17

Preparation of oral suspension

	Gram
4OH OPB (Example 7)	10
Carboxymethyl cellulose	1.5
Sorbitol	200
Sodium benzoate	1.0
Orange essence	0.3
Apricot essence	0.7
Ethanol	50
Water	236.5

Carboxymethyl cellulose, sorbitol and sodium benzoate are dissolved in water with stirring for 2 hours. A solution of the essences in ethanol is added. 4-OH OPB is screened through a 0.15 mm sieve and dispersed in the solution under vigorous stirring. The suspension (10 gram) is filled in a 20 ml tube. Each tube contains 200 mg 4-OH OPB.

EXAMPLE 18

Mouse toxicity

20g mice were given single doses of 4OH-OPB (20 mM in DMSO) intraperitoneally. Doses of 1 to 100 μM (in ECF), corresponding to 0.29 to 29 μM/kg bodyweight, produced no toxic effect. Furthermore, injection of 4OH-OPB could be increased to 2000 mg/kg (corresponding to 20 mM in the extracellular fluid) before the mice started to die (6 out of 10 died at 2000 mg/kg). Thus the concentrations that effectively inhibit HIV replication in cell cultures are up to 200000 times lower than the lethal dose in mice.

Claims

1. The use of an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in therapy or prophylaxis.

2. A method of treatment of the human or non-human body to combat an inflammatory or viral disease, which method comprises administering to said body an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

3. A method as claimed in claim 2 comprising administering said optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof in combination with another antiviral agent.

4. A method as claimed in claim 3 wherein said additional antiviral agent is at least one antiviral agent selected from a reverse transcriptase inhibitor and a protease inhibitor.

5. A method as claimed in claim 3 wherein said additional antiviral agent is an agent selected from the group of AZT, indinavir, nevirapine and 2',3'-dideoxyinosine (daI).

6. A method as claimed in any of claims 2 to 5 wherein said disease is a disease caused by a pathogen from the

group of togaviridea, reoviridea, picornaviridea, hantaviridea, orthomyxoviridea, paramyxoviridea, mononegaviralis, viral hepatitis, haemorrhagic fevers, flaviviridea, viral encephalitis, coronaviridea, calciviridea, adenoviridea, papovaviridea, arboviridea, pox virus, rhabdoviridea, arenaviridea HIV-1, HIV-2, HTLV-I, HTLV-II and herpes viruses.

7. A method of combatting HIV infection which comprises administering to an HIV-infected patient a T-lymphocyte growth suppressing agent in an amount sufficient to suppress T-lymphocyte growth in said patient for a period sufficient to reduce the T-lymphocyte concentration in the lymphatic system in said patient by at least 25% said administration being repeated at intervals of at least 3 months.

8. A method of combatting HIV infection as claimed in claim 6 wherein said T-lymphocyte growth suppressing agent is a pyrazolidinol.

9. A method as claimed in claim 7 or claim 8 wherein said interval is at least 9 months.

10. A method as claimed in any of claims 7 to 9 wherein a 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof is administered in a daily dose of 0.1 to 10 μmol/kg bodyweight.

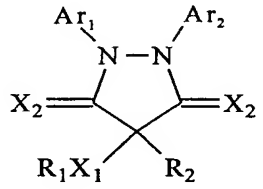
11. A pharmaceutical composition comprising an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, together with at least one pharmaceutically acceptable

carrier or excipient.

12. A pharmaceutical composition as claimed in claim 11 additionally comprising another antiviral agent.

13. An optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

14. A compound of formula I



(I)

(where each X_2, which may be the same or different is O or S,
X_1 is O, OO or S,
R_1 is hydrogen or a hydroxyl or thiol protecting group,
R_2 is hydrogen or a carbon attached organic group containing up to 10 carbons, and each of
Ar_1 and Ar_2, which may be the same or different, is a homo or heterocyclic aromatic group) or a salt thereof.

15. A compound of claim 14 wherein R_1, R_2, X_1, X_2, Ar_1 and Ar_2 are as defined in claim 14, providing that if X_1 and each X_2 is O, the remaining groups do not correspond to the following table:

R_2	R_1	Ar_1	Ar_2
H	H	H	C_6H_5
H	H	C_6H_5	C_6H_5
CH_3	H	H	C_6H_5
CH_3	H	H	$-CH_2-C_6H_5$
CH_3	H	H	$p-CH_3O-C_6H_4$
CH_3	H	H	$p-Cl-C_6H_4$
C_2H_5	H	H	C_6H_5
C_2H_5	H	C_6H_5	C_6H_5
C_2H_5	H	H	N-methyl-piperidin-4-yl
iC_3H_7	H	H	C_6H_5
nC_3H_7	H	H	C_6H_5
nC_3H_7	H	C_6H_5	C_6H_5
nC_3H_7	H	H	5-phenyl-triazol-1-yl
C_4H_9	H	H	C_6H_5
C_4H_9	H	C_6H_5	C_6H_5
C_4H_9	H	C_6H_5	$p-OH-C_6H_4$
C_4H_9	OH	C_6H_5	C_6H_5
C_4H_9	OH	C_6H_5	$p-OH-C_6H_4$
C_4H_9	H	H	N-methyl-piperidin-4-yl
C_5H_{11}	H	H	C_6H_5
C_5H_{11}	H	C_6H_5	C_6H_5
C_5H_{11}	H	H	5-phenyl-triazol-1-yl
Cyclohexyl	H	H	C_6H_5
Phenyl	H	H	C_6H_5
Phenyl	H	C_6H_5	C_6H_5
Benzyl	H	H	C_6H_5
Benzyl	H	C_6H_5	C_6H_5
$CH_3CO(CH_2)_2$	H	C_6H_5	C_6H_5
$(CH_3)_2C=CH-$	H	C_6H_5	C_6H_5
$(CH_2)_2C=CHCH_2$	H	C_6H_5	C_6H_5
$C_6H_5SCH_2CH_2$	H	C_6H_5	C_6H_5
Pyrrolidin-1-yl	H	C_6H_5	C_6H_5
Piperidin-1-yl	H	C_6H_5	C_6H_5
Morpholin-4-yl	H	C_6H_5	C_6H_5

16. A compound as claimed in claim 14 or claim 15 wherein one X_2 group is S.

17. A compound as claimed in any of claims 14 to 16 wherein X_1 is O.

18. A compound as claimed in any of claims 14 to 17 wherein R_1 is acyl.

19 A compound as claimed in any of claims 14 to 18 wherein R_1 is hydrogen.

20. A compound as claimed in any of claims 14 to 19 wherein one of Ar_1 and Ar_2 is Ph and the other is 4-hydroxyphenyl.

21. A compound as claimed in claim 14 wherein each X_2 is oxygen, R_1X_1 is HO or $CH_3CO.O$, each of Ar_1 and AR_2, which may be the same or different is optionally halo or hydroxy substituted phenyl, and R_2 is C_{1-6} alkyl or alkenyl, or a salt thereof.

22. A compound as claimed in any of claims 14 to 21 for use as a medicament.

23. 4-Butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione for use as a medicament.

24. A method of treatment of the human or non-human body to combat an autoimmune disease or tissue rejection, which method comprises administering to said body an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

25. A method of claim 24 wherein said disease is selected from Addison's disease, Behçet's syndrome, diabetes mellitus, haemolytic anaemia, lupus erythematosus, multiple sclerosis, myasthenia gravis, pernicious anaemia, polyglandular deficiency, polymyositis, dermatomyositis, testicular failure, thrombocytopenic purpura, Crohns disease, ulcerative colitis and rheumatoid arthritis.

26. A method of claim 24 wherein said tissue rejection is tissue rejection following transplant.

FIG. 1

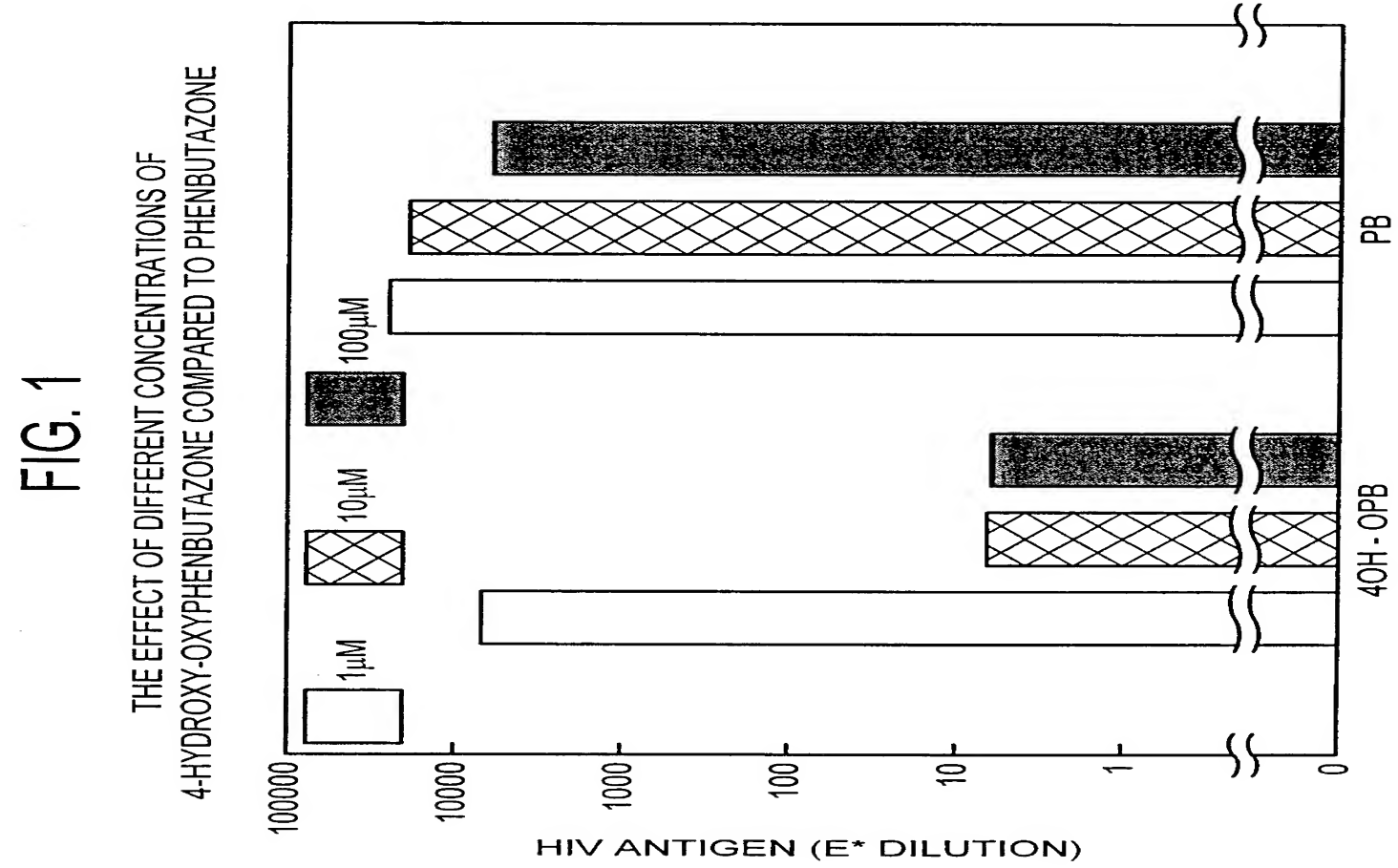

THE EFFECT OF DIFFERENT CONCENTRATIONS OF
4-HYDROXY-OXYPHENBUTAZONE COMPARED TO PHENBUTAZONE
1μM
10μM
100μM
100000
10000
1000
100
10
1
0
HIV ANTIGEN (E* DILUTION)
4OH - OPB
PB

FIG. 2

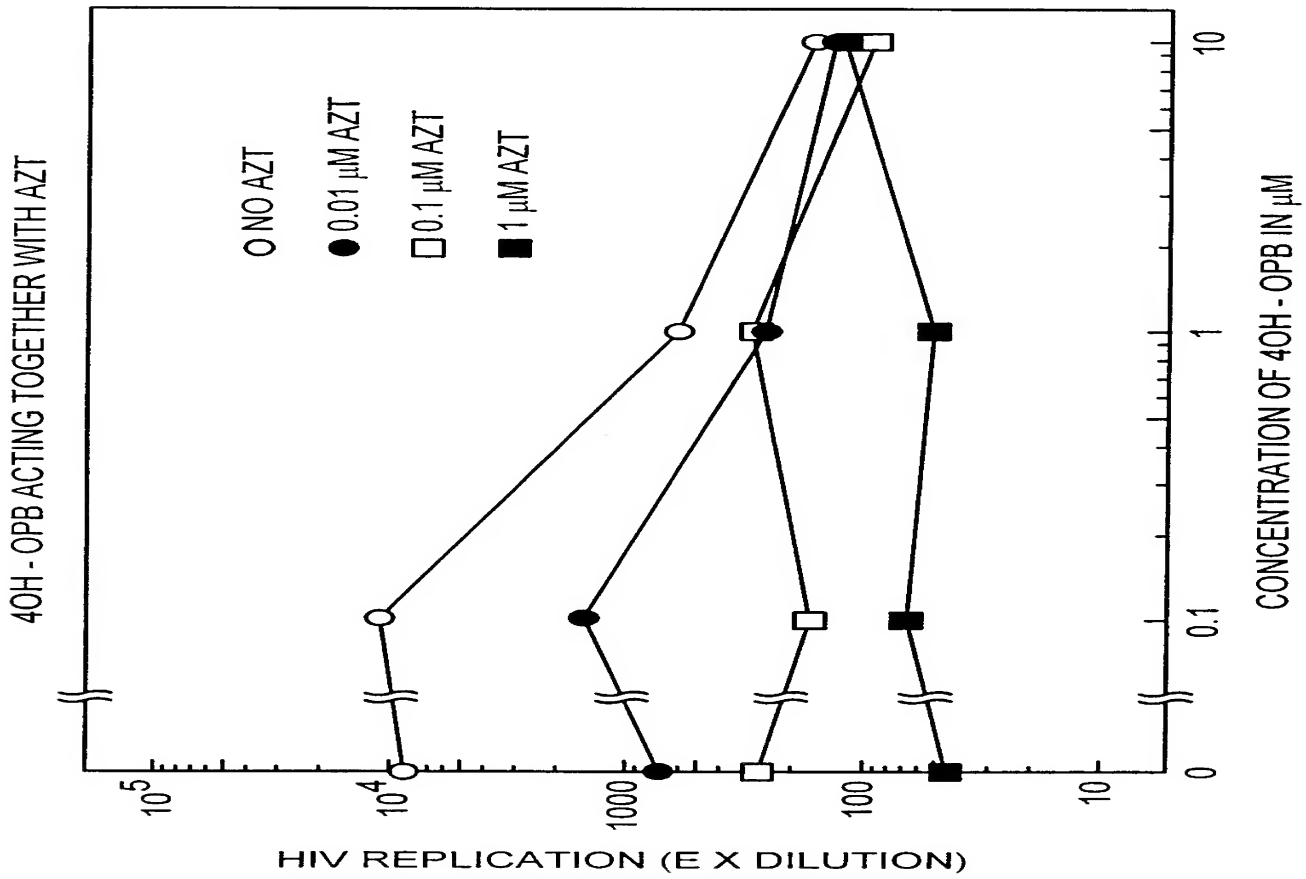

4OH - OPB ACTING TOGETHER WITH AZT
O NO AZT
● 0.01 µM AZT
□ 0.1 µM AZT
■ 1 µM AZT
HIV REPLICATION (E X DILUTION)
10^5
10^4
1000
100
10
0
0.1
1
10
CONCENTRATION OF 4OH - OPB IN µM

FIG. 3

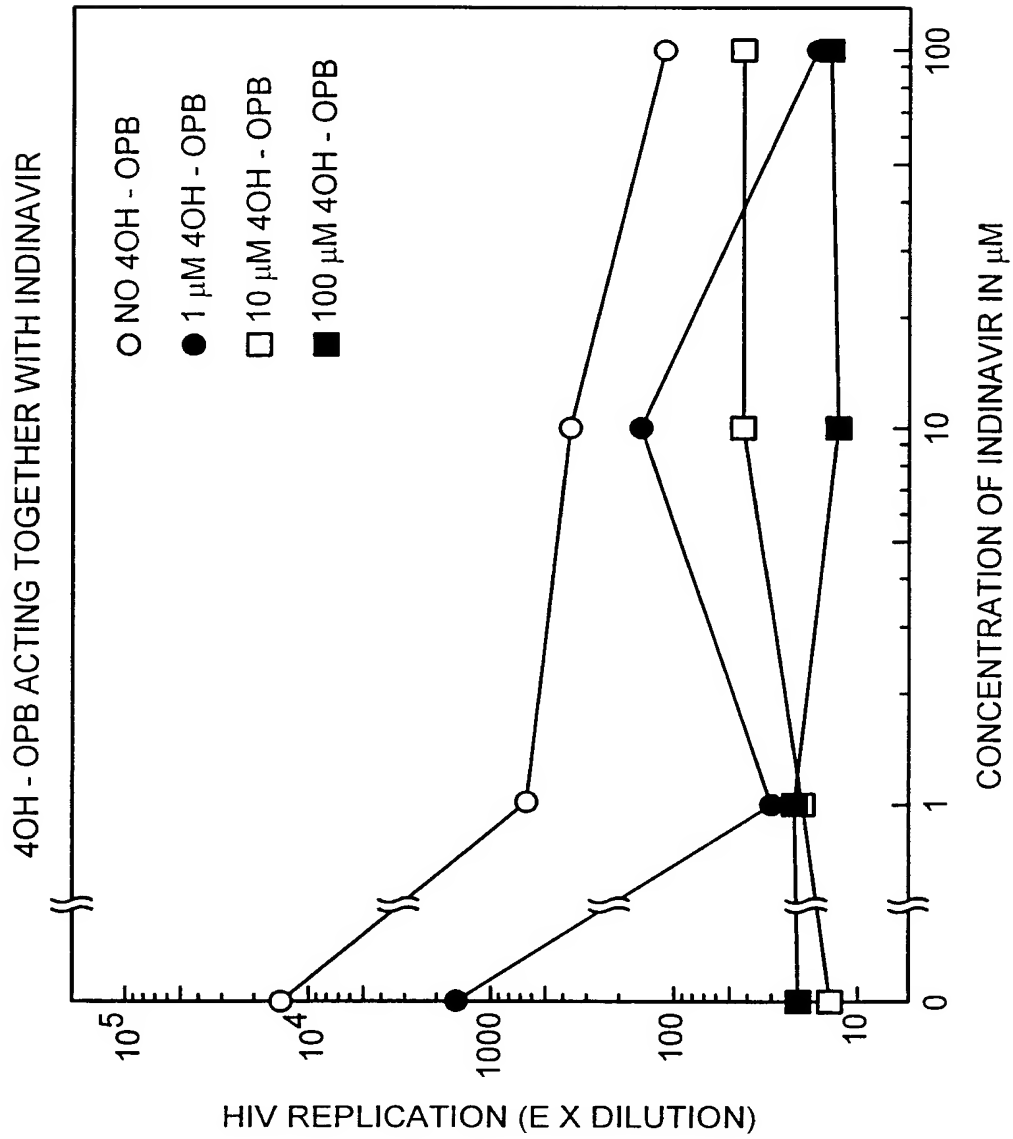

4OH - OPB ACTING TOGETHER WITH INDINAVIR
O NO 4OH - OPB
● 1 μM 4OH - OPB
□ 10 μM 4OH - OPB
■ 100 μM 4OH - OPB
HIV REPLICATION (E X DILUTION)
10^5
10^4
1000
100
10
0
1
10
100
CONCENTRATION OF INDINAVIR IN μM

FIG. 4

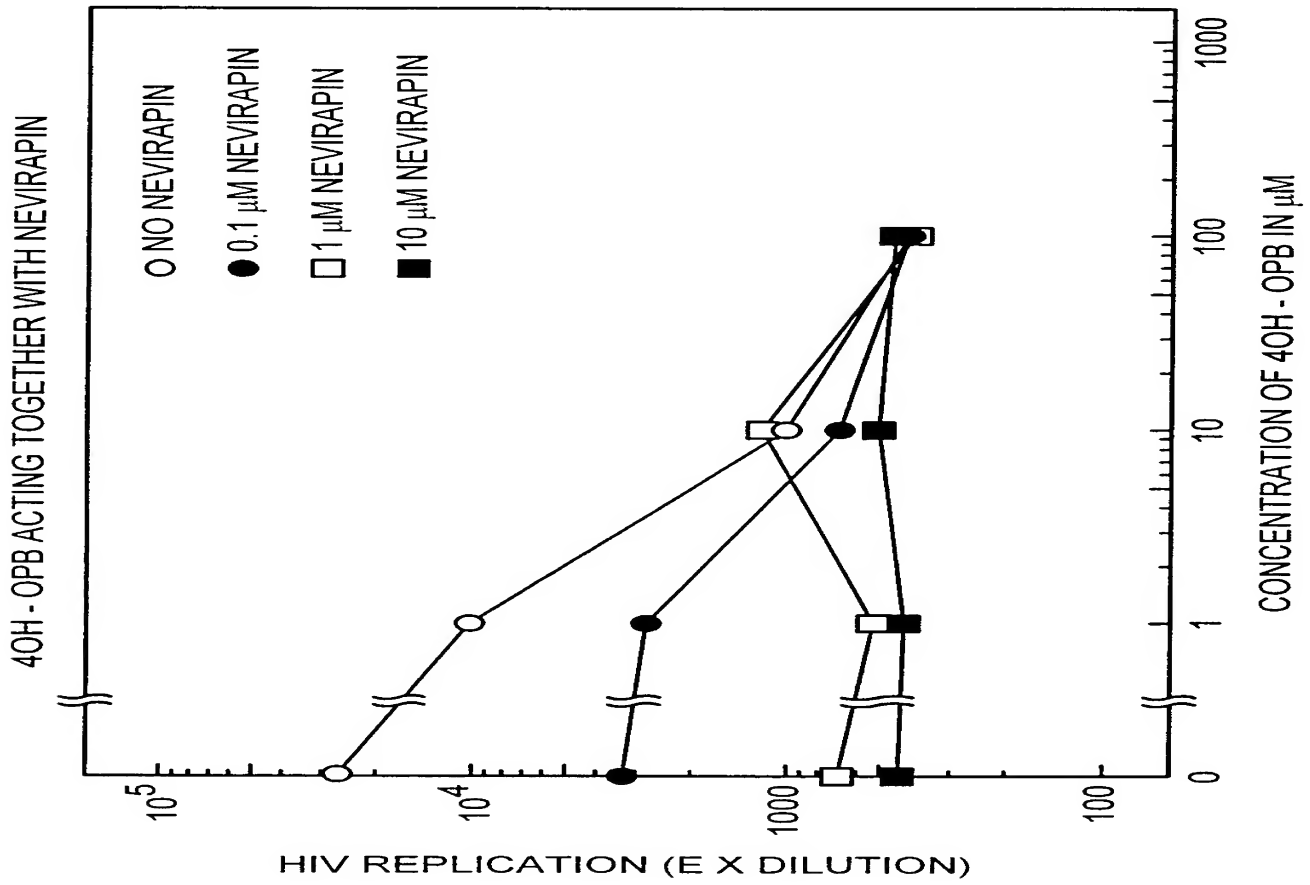
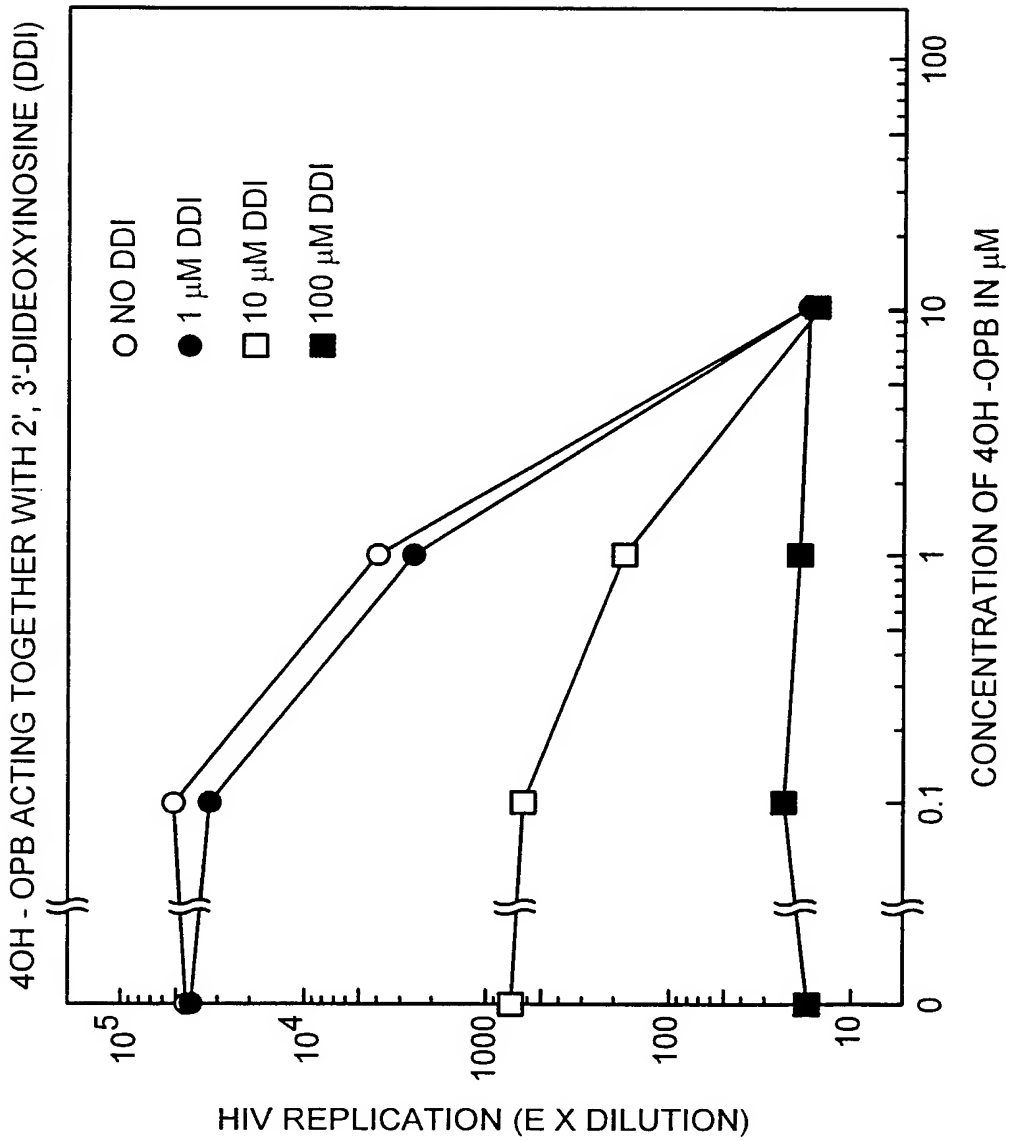

4OH - OPB ACTING TOGETHER WITH NEVIRAPIN
O NO NEVIRAPIN
● 0.1 μM NEVIRAPIN
□ 1 μM NEVIRAPIN
■ 10 μM NEVIRAPIN
HIV REPLICATION (E X DILUTION)
10^5
10^4
1000
100
0
1
10
100
1000
CONCENTRATION OF 4OH - OPB IN μM

FIG. 5


4OH - OPB ACTING TOGETHER WITH 2', 3'-DIDEOXYINOSINE (DDI)
O NO DDI
● 1 μM DDI
□ 10 μM DDI
■ 100 μM DDI
10^5
10^4
1000
100
10
HIV REPLICATION (E X DILUTION)
0
0.1
1
10
100
CONCENTRATION OF 4OH -OPB IN μM

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 00/02513

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/32 C07D231/30 A61K31/4152 A61P31/08 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. F. HUGHES ET AL.: MOLECULAR PHARMACOLOGY, vol. 34, no. 2, 1988, pages 186-93, XP000925977 page 186, summary; page 191, scheme 1; page 191-192 ---	1,2,13, 14,16, 17,19, 21,22
X	P. S. PORTOGHESE ET AL.: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 63, no. 3, 1975, pages 748-55, XP000925976 page 748 page 751 -page 752 page 754, figure 2 --- -/--	13,14, 17,20,22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 2000	06/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	R. WACHOWIAK: POL. J. PHARMACOL. PHARM., vol. 30, no. 6, 1978, pages 833-43, XP000925975 page 841, compound 6 ---	13-15, 17,19
X	J. X. DE VRIES ET AL.: JOURNAL OF CHROMATOGRAPHY, vol. 277, 1983, pages 408-13, XP000925974 page 408, compound 7 ---	13-15, 17,19
X	H. FABRE ET AL.: ANALYST, vol. 110, no. 1, November 1985 (1985-11), pages 1289-93, XP000925972 page 1290, table 1, compounds I and IV ---	13,14, 17,19
X	S. ICHIHARA ET AL.: BIOCHEMICAL PHARMACOLOGY, vol. 35, no. 22, 1986, pages 3935-9, XP000925971 page 3937, figures 2 and 3; page 3938, figure 5 ---	13,14, 17,19
X	G. FACCHINI ET AL.: BOLL. CHIM. PHARM., vol. 126, no. 6, 1987, pages 244-5, XP000925970 page 244, compound 4 ---	13,14, 17,19
X	D. RAHTZ ET AL.: EUR. J. MED. CHEM. - CHIM. THER., vol. 17, no. 5, 1982, pages 429-32, XP000925964 page 430, right-hand column, compound 13; page 432, left-hand column, lines 1-5 ---	13,14, 17,19
X	M. PETERKOVA ET AL.: CESKOSLOVENSKA FARMACIE, vol. 24, no. 3, 1975, pages 128-32, XP000925980 page 130, right-hand column, chemical formula ---	13,14, 17,19
X	O. AKI ET AL.: CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 20, no. 9, 1972, pages 1862-8, XP000925979 page 1864, table III, compounds 15-23 ---	13-15, 17,19
X	M. WOODRUFF ET AL.: AUSTRALIAN JOURNAL OF CHEMISTRY, vol. 28, no. 2, 1975, pages 421-6, XP000952038 page 422, formula (2) and corresponding definitions in the text --- -/--	13,14, 17,19

2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02513

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	R. T. COUTTS ET AL.: CANADIAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 2, no. 1, 1967, pages 22-4, XP000952039 page 22, formula I ---	13,14, 17,19
X	CHEMICAL ABSTRACTS, vol. 54, no. 21, 10 November 1960 (1960-11-10) Columbus, Ohio, US; abstract no. 22587h, column 22587; XP002150571 22587h, 22588d & G. ADEMBRI ET AL.: GAZZ. CHIM. ITAL., vol. 89, 1959, pages 700-9, ---	13,14, 17,19
X	CHEMICAL ABSTRACTS, vol. 51, no. 14, 25 July 1957 (1957-07-25) Columbus, Ohio, US; abstract no. 10491d, column 10491; XP002150572 10491h, 10491i, 10492a, 10492b & K. M. HAMMOND ET AL.: J. CHEM. SOC., 1957, pages 1062-7, ---	13,14, 17,19
A	DE 20 22 712 A (DR. THIEMANN GMBH CHEM.-PHARM. FABRIK) 25 November 1971 (1971-11-25) claims 1,2 ---	1,2,11, 13-15,22
A	US 3 629 282 A (NEGREVERGNE GEORGES) 21 December 1971 (1971-12-21) abstract; claim 1 ---	1,2,11, 13-15,22
A	US 4 956 377 A (MIESCH JEAN-OLIVIER) 11 September 1990 (1990-09-11) cited in the application claims ---	1,2,6-8, 24
A	US 4 169 147 A (BODOR NICHOLAS S ET AL) 25 September 1979 (1979-09-25) cited in the application abstract & US 4 139 709 A 13 February 1979 (1979-02-13) cited in the application & US 4 117 232 A cited in the application & US 4 036 845 A cited in the application & US 3 957 803 A cited in the application --- -/--	1,2,11

2

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/GB 00/02513

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 968 219 A (RAHTZ DIETER ET AL) 6 July 1976 (1976-07-06) cited in the application claims 1,13,14 -----	1,2,11

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Intern ...al Application No
PCT/GB 00/02513

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2022712 A	25-11-1971	NONE	
US 3629282 A	21-12-1971	DE 1470148 A	04-06-1969
		FI 43993 B	30-04-1971
		FI 48735 B	02-09-1974
		NO 117481 B	18-08-1969
		NO 117482 B	18-08-1969
		US 3833729 A	03-09-1974
		US 3487046 A	30-12-1969
		US 3787389 A	22-01-1974
		US 3790558 A	05-02-1974
US 4956377 A	11-09-1990	FR 2593703 A	07-08-1987
		EP 0285730 A	12-10-1988
		JP 63267719 A	04-11-1988
US 4169147 A	25-09-1979	US 3957803 A	18-05-1976
		US 4036845 A	19-07-1977
		AU 1006376 A	14-07-1977
		DE 2600325 A	08-07-1976
		FR 2296416 A	30-07-1976
		GB 1490952 A	09-11-1977
		JP 51091261 A	10-08-1976
		US 4139709 A	13-02-1979
		US 4117232 A	26-09-1978
US 3968219 A	06-07-1976	DE 2436882 A	19-02-1976
		AT 353261 B	12-11-1979
		AT 488077 A	15-04-1979
		AT 344689 B	10-08-1978
		AT 583675 A	15-12-1977
		AU 8332175 A	27-01-1977
		BE 831855 A	29-01-1976
		CA 1062264 A	11-09-1979
		CH 617927 A	30-06-1980
		CH 617926 A	30-06-1980
		CS 197253 B	30-04-1980
		CS 197252 B	30-04-1980
		DD 122533 A	12-10-1976
		DK 344375 A,B,	30-01-1976
		ES 439810 A	16-04-1977
		FR 2280374 A	27-02-1976
		GB 1519498 A	26-07-1978
		HU 170518 B	28-06-1977
		IE 41639 B	13-02-1980
		IL 47768 A	31-10-1979
		JP 51036452 A	27-03-1976
		NL 7509060 A	02-02-1976
		SE 415252 B	22-09-1980
		SE 7508543 A	30-01-1976
		SU 593662 A	15-02-1978